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Substituent effects on axial chirality in 1-aryl-3,4-dihydroisoquinolines: controlling the rate of bond rotation

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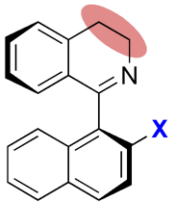
Josep Mas Roselló, Samantha Staniland, Nicholas J. Turner and Jonathan Clayden*



3,4-Dihydroisoquinolines

X = Br, I: Marginally atropisomeric

X = OTf: Atropisomeric

X = $P(O)Ph_2$: Atropisomeric

Substituent effects on axial chirality in 1-aryl-3,4-dihydroisoquinolines: controlling the rate of bond rotation.

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ABSTRACT

A series of 1-aryl-3,4-dihydroisoquinolines (DHIQs) were synthesized and their barriers to bond rotation were determined by means of VT-NMR, dynamic HPLC or racemization studies. Although they all presented lower rotational stability than the related 1-arylisoquinolines (such as QUINAP), certain 1-aryl-DHIQ structures had a sufficiently high barrier to bond rotation to show axial chirality. These compounds included 1-(2-triflyl-1-naphthyl)-4,5-dihydroisoquinoline **4h** and 1-(2-diphenylphosphanyl-1-naphthyl)-4,5-dihydroisoquinoline **4i**. This discovery opens the door to the development of a new group of axially chiral N,P ligands for asymmetric synthesis and also potentially to new strategies for the synthesis of axially chiral 1-arylisoquinolines.

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1. Introduction

The majority of axially chiral compounds are biaryls, whether biphenyls or binaphthyls[1] or their heterocyclic counterparts.[2] Particularly valuable are biaryls containing the isoquinoline ring,[3] which function as atropisomeric chiral ligands because their basic nitrogen atom allows bidentate coordination in P,N ligands[4] such as QUINAP (Figure 1). QUINAP is the ligand of choice in many asymmetric reactions,[5] including asymmetric hydroborations, diborations, dipolar cycloadditions, conjugate additions and additions to iminium ions.

Configurational stability about the biaryl axis in 1-naphthylisoquinolines depends on the substituent at the 2-position of the naphthyl ring. The 2-unsubstituted structure **1a** is configurationally unstable at room temperature, with an estimated half-life for racemization of 13 min at –20 °C.[6] In contrast, the amino-substituted structure **1b** is configurationally stable, with a barrier to bond rotation of 125.4 kJ mol^{-1}.[7] The more substituted compounds **1c**[8] and QUINAP **1d**[5] showed no sign of racemization on extended heating.

One report of a related partially saturated structure,[9] 3,4-dihydroisoquinoline **2a**, suggests that its barrier to rotation is too low to permit resolution, but the rate of bond rotation was not quantified. A chiral derivative **2b** nonetheless displayed separable diastereoisomeric atropisomers, but again no barrier was reported. The diastereoisomers of the corresponding triflate **2c** were not separable. Related 1-aryl-3,4-dihydroisoquinolines are of medicinal interest as potent neuroprotectors.[10]

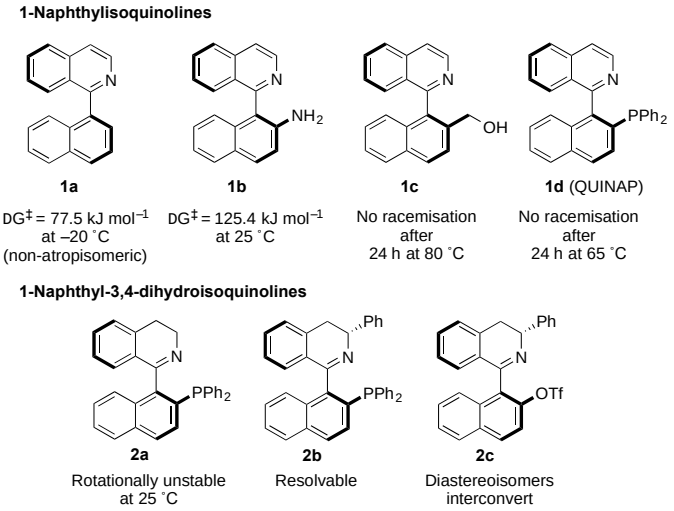


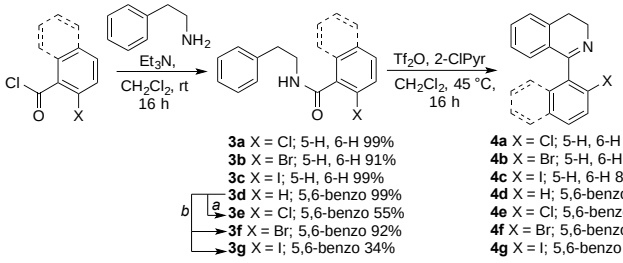
Figure 1. Bond rotations in 1-naphthylisoquinolines and their 3,4-dihydroisoquinoline analogues.

Although 1-aryl-DHIQs are more conformationally flexible than the related fully aromatic isoquinolines, and evidently display lower barriers to rotation, they do show potential for atropisomerism and could provide a new class of axially chiral compounds with potential applications as ligands or building blocks for asymmetric synthesis or chiral ligands. QUINAP is typically produced in enantiomerically pure form by classical resolution.[4,5,11] Methods have also been reported for its asymmetric synthesis by dynamic resolution techniques, relying of the control of the kinetics and thermodynamics of bond rotation.[12] Further interest arises from the possibility of using redox interconversions between QUINAP and its partially saturated analogues to control dynamic resolution processes. In this paper we describe our investigation into the control of rotational barriers in 1-aryl-3,4-dihydroisoquinolines as a potential new class of non-biaryl atropisomers.[13]

2. Results and discussion

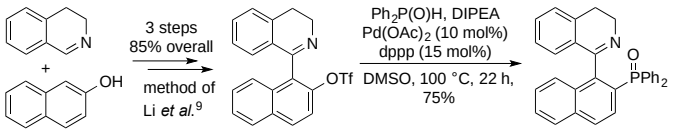
2.1. Starting materials

A range of racemic 1-aryl-DHIQs halogenated at the 2-position of the 1-aryl ring (**4a-g**) were readily synthesized in high yields from the corresponding amides **3a-g** by the modified Bischler-Napieralski cyclisation reported by Movassaghi *et al*.[14] Amide starting materials for the cyclisation were made either by acylation of phenethylamine with available 2-halobenzoyl chloride or 1-naphthoyl chloride (giving **3a-d**). The remaining amides **3e-f** were made by halogenation of **3d** by means of rhodium[15] or palladium[16] catalyzed C-H activation reactions, with the amide as a directing group for chemoselective halogenation at the *ortho* position of the 1-naphthyl ring.



Scheme 1. Synthesis of 1-acyl-3,4-dihydroisoquinolines. Reagents: (*a*) NCS, $Pd(OAc)_2$ (5 mol%), TfOH, $Na_2S_2O_8$, DCE, 80 °C, 32 h; (*b*) NBS/NIS, $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), PivOH, DCE, 70 °C, 18 h.

In addition, triflyl-substituted DHIQ **4h** was made by the method of Li *et al*.[9] (Scheme 2) and converted into phosphine oxide **4i** by palladium-catalyzed coupling[17] with $Ph_2P(O)H$.

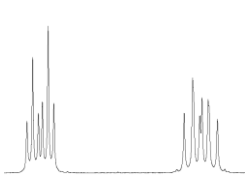
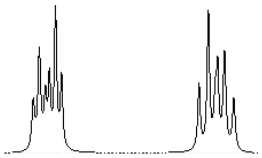
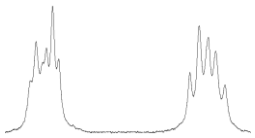
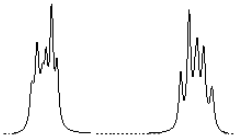
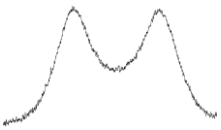
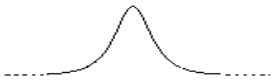


Scheme 2. Synthesis of substituted 1-naphthyl-3,4-dihydroisoquinolines.

2.2. Determination of the barriers to bond rotation in variously substituted DHIQs

Variable temperature NMR (VT-NMR) studies were carried out to estimate the rate of bond rotation about the Ar-DHIQ axis of the less hindered group of compounds **4a-d**. The ^1H NMR line shapes of the signals arising from the potentially diatereotopic protons in the $–CH_2–CH_2–$ unit of the DHIQ were monitored in $CDCl_3$ at temperatures between –30 °C and +30 °C. The line shapes were modelled using the commercial program gNMR.[18,19] Table 1 illustrates (for one example, bromo-substituted **4b**) the modelled and observed line shapes of the two diastereotopic methylene protons (H_A, H_B) α to the nitrogen atom at a series of temperatures, and shows the estimated rate constant, *k*, for their exchange.

Table 1. Line shape analysis in the VT NMR study of **4b**

T / °C	Experimental line shape	Modelled line shape	k / s^{-1}
-30			1
-10			20
0			57
20			220
30			550

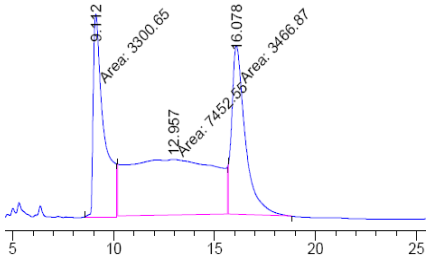
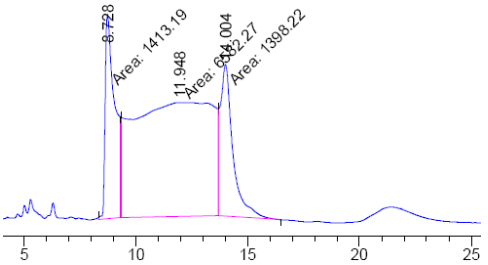
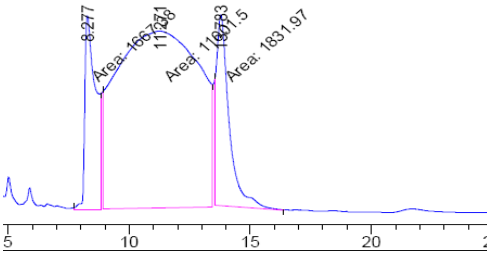
These rates were analysed using the Eyring equation, allowing calculation of the barrier to bond rotation ($\Delta G^{\ddagger}$) and an estimation the half life for racemization ($t_{½}^{rac}$) of **4a-d** in solution at a given temperature.

It was not possible to use VT-NMR to derive a barrier to rotation of the more sterically encumbered substrate **4e** since no line broadening or coalescences were observed even at 120 ºC in 1,2-dichlorobenzene-d_4. Rotationally restricted compounds with half lives for racemization falling into the timescale of minutes at ambient temperature are typically difficult to analyse by VT-NMR for this reason, but this racemization profile is ideal for investigation by dynamic (variable temperature) HPLC (DHPLC) on a chiral stationary phase.[13a,19-21]

DHPLC studies were undertaken using DHIQs **4e-g**. For **4e**, all the chiral stationary phases and eluents we explored showed a single peak, even on cooling the column to 0 ºC. Although no numerical values for the barrier to rotation of **4e** were obtained, we assume therefore that chloro-substituted **4e** rotates freely (that is, on a time scale of seconds or less) at room temperature.

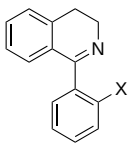
More information was obtained from **4f**, which showed peak shapes characteristic of racemisation on the timescale of elution on a (*R,R*)-Whelk-O1 stationary phase, eluting with *n*-hexane/isopropanol (60:40). Peak profiles were monitored at 20, 30 and 40 °C (Table 2) and the parameters obtained from the profiles were entered into the Unified Equation for Dynamic Chromatography.[19,20] From this equation, the rates of interconversion of the two enantiomers of **4f** were calculated. An Eyring plot of this data revelaed that **4f** was almost atropisomeric[22] at 25 ºC ($\Delta G^{\ddagger}_{298}$ = 92.6 kJ mol^{-1}; $t_{½}^{rac}$ = 900 s).

Table 2. Dynamic HPLC profiles for **4f** on the (*R,R*)-Whelk-O1 chiral stationary phase, eluting with *n*-hexane/isopropanol (60:40).

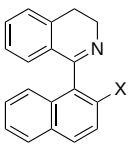
T / ºC	Observed peak shape	k / 10^3 s^{-1}
20		4.5
30		7.1
40		9.9

Similar approximate analysis of the DHPLC trace of **4g** around 0 °C indicated that **4g** had a lower barrier to rotation than **4f**. The replacement of a bromine atom by a bulkier iodine atom at the naphthyl ring's *ortho* position did not increase rotational stability at the Ar-DHIQ bond. Presumably the bigger atomic radius of iodine is countered by the longer bond length of C–I (a similar effect is well established in *A* values).[23]

Table 3. Summary of kinetic parameters for bond rotations in 1-arylDHIQs



4a-4c



4d-4i

Cpd.	X =	$\Delta H^{\ddagger}$ / kJ mol^{-1}	$\Delta S^{\ddagger}$ / J mol^{-1} K^{-1}	$\Delta G^{\ddagger}_{298}$ / kJ mol^{-1}	$t_{1/2}^{rac}{}_{298}$[a]
4a	Cl	56.6	–9	59.2	≈ 10^{-3} s
4b	Br	50.7	–26	58.4	< 10^{-3} s
4c	I	64.0	+20	57.9	< 10^{-3} s
4d	H	55.1	+1	54.7	≈ 10^{-4} s
4e	Cl	–	–	< 90[b]	< 5 min
4f	Br	34.6	–195	92.6	15 min
4g	I	–	–	81.9[c]	< 1 min[d]
4h	OTf	10.7	+14.5	103.1	36 days
4i	$P(O)Ph_2$	–	–	>>100	>25 days

[a]Estimated half life for racemization. [b]Not determined (achiral by HPLC). [c]Determined at 0 °C. Insufficient data to allow calculation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. [d]Assuming $\Delta S^{\ddagger} = 0$.

In marked contrast, compound **4h** bearing an O-triflyl group at the *ortho* position of the naphthyl core showed no signs of racemization on the timescale of elution from a chiral stationary phase at room temperature. The enantiomers of **4h** were therefore separated on a small scale by semi-preparative HPLC, and their interconversion was studied in isopropanol at three different temperatures: 43, 50 and 58 °C. The decrease in ee over time was monitored and plots of ln(ee) against time gave for the rate of racemisation at each temperature. Using the Eyring equation, values of $\Delta G^{\ddagger}$ at room temperature could be derived along with $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ (Table 3). From these values we estimate **4h** to have a half life for racemization of at least one month in solution.

We envisaged that a phosphine oxide substituent at the naphthyl 2-position might further increase the barrier to rotation, and possibly provide a valuable contrast to dihydro-QUINAP (**2a**, Figure 1), which was reported to be rotationally unstable at room temperature. Indeed, chiral HPLC traces of rac-**4i** showed no racemisation on-column at 50 ºC, suggesting a half life for racemization at this temperature of at least 30 min, and hence a barrier to bond rotation of >>100 kJ mol^{-1}. Phosphine oxide **4i** is thus the first reported rotationally stable 1-aryl-3,4-dihydroisoquinoline. Interestingly, tertiary phosphine oxide N,P-ligands have been found to display higher catalytic activities in, for example, olefin hydroformylation reactions than their tertiary phosphine analogues,[23] suggesting the possible use of **4i** itself as a chiral ligand.

3. Conclusion

A series of rotationally restricted and axially chiral 1-aryl-3,4-dihydroisoquinolines (1-aryl-DHIQ) were readily synthesized using inter or intramolecular electrophilic aromatic substitution chemistry. Their barriers to rotation about their Ar–CN bond were determined by means of VT-NMR, dynamic HPLC and racemization studies. Despite significantly greater molecular flexibility than the related 1-aryl-isoquinolines, two 1-naphthyl DHIQs showed stable axial chirality at ambient temperature. Notably, triflate, as a pseudohalide, provided a much greater barrier to bond rotation than the equivalent halides (Br, I). This first report of atropisomeric 1-aryl-3,4-dihydroisoquinolines opens the door to the development of new axially chiral 3,4-dihydroisoquinoline-containing N,P ligands for asymmetric synthesis.

4. Experimental

4.1. General procedure for amide (3a-d) formation from 2-phenylethylamine and an acyl chloride.

2-Phenylethylamine (1 equiv) and Et_3N (2 equiv) were added to a solution of the acyl chloride (1 equiv) in dichloromethane and the reaction mixture was stirred for 16 h at room temperature. The solvent and the excess Et_3N were removed under reduced pressure. The residue was suspended in water and extracted twice in EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used without any further purification. The experimental data for 2-chloro-*N*-phenethylbenzamide **3a**,[25a] 2-bromo-*N*-phenethylbenzamide **3b**,[25b] 2-iodo-*N*-phenethylbenzamide **3c**[25c] and *N*-phenethyl-1-naphthamide **3d**[25d] were consistent with the literature.

4.1.1. 2-Chloro-*N*-phenethyl-1-naphthamide (3e)

Compound **3e** was prepared according to the method of Rao *et al.*[16] *N*-Phenethyl-1-naphthamide **3d** (100 mg, 0.36 mmol), NCS (64 mg, 0.48 mmol), $Pd(OAc)_2$ (6 mg, 0.018 mmol, 5 mol%) and sodium persulfate (174 mg, 0.72 mmol) were dissolved in dry 1,2-DCE (2 mL) in a flame-dried sealed vial under argon. The mixture was degassed under reduced pressure and the vessel filled with argon. TfOH (110 mg, 0.72 mmol) was added dropwise. The reaction mixture was stirred for 32 h at 80 ºC. After cooling to room temperature, the reaction was quenched by adding saturated aqueous $NaHCO_3$. The reaction mixture was diluted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure and the crude product was purified by flash column chromatography (80:20 Pet. Ether:EtOAc) to afford the title compound as a yellow oil (62 mg, 55%); **3e**: $\mathbf{R_f}$ (70:30 Pet. Ether:EtOAc) 0.45; **IR (film, cm^{-1})**: ν_{max} = 3268, 1636 (C=O), 821; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.90 (1 H, dd, *J*=6.2, 3.4 Hz, Ar*H*), 7.80 (1 H, dd, *J*=8.2, 0.9 Hz, Ar*H*), 7.63 (1 H, dd, *J*=7.6, 1.3 Hz, Ar*H*), 7.51 - 7.47 (2 H, m, 2xAr*H*), 7.45 - 7.42 (1 H, m, Ar*H*), 7.34 - 7.29 (3 H, m, 3xAr*H*), 7.23 (2 H, m, 2xAr*H*), 5.81 (1 H, br. s., N*H*), 3.84 (2 H, dt, *J*=7.1, 6.3 Hz, NHCH_2CH_2Ph), 3.01 ppm (2 H, t, *J*=7.1 Hz, NHCH_2CH_2Ph); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.0 (C=O), 138.8 (Ar*C*), 135.4 (Ar*C*), 134.3 (Ar*C*), 130.4 (Ar*C*), 130.2 (Ar*C*), 130.1 (Ar*C*), 129.0 (2xAr*C*), 128.7 (Ar*C*), 128.6 (Ar*C*), 127.9 (Ar*C*), 127.7 (Ar*C*), 126.9 (Ar*C*), 126.5 (Ar*C*), 126.2 (Ar*C*), 125.5 (Ar*C*), 41.2 (NH*C*H_2CH_2Ph), 35.2 (NHCH_2*C*H_2Ph) ppm; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{16}ClNONa$ [M+Na$^+$]: 332.0813, found: 332.0820.

4.1.2. 2-Bromo-*N*-phenethyl-1-naphthamide (3f)

Compound **3f** was prepared according to the method of Glorius *et al.*[15] $[RhCp^*Cl_2]_2$ (0.058 g, 0.09 mmol, 2.5 mol%), $AgSbF_6$ (0.127 g, 0.36 mmol, 10 mol%) and PivOH (0.5 ml, 4.00 mmol). 1,2-DCE (18 mL), *N*-phenethyl-1-naphthamide **3d** (1.000 g, 3.63 mmol) and NBS (0.970 g, 5.45 mmol) were added under nitrogen to a flame-dried round-bottom flask. The reaction mixture was degassed under reduced pressure, the vessel filled with nitrogen, and the mixture heated at 65 ºC for 18 h. The mixture was cooled to room temperature, diluted with EtOAc and filtered through a short pad of silica gel and eluted with EtOAc. After removal of solvent under reduced pressure, the crude product was purified by flash column chromatography (70:30 Pet. Ether:EtOAc) to afford the title compound as a white solid (1.184 g, 92%); **3f**: $\mathbf{R_f}$ (50:50 Pet. Ether:EtOAc) 0.5; **m.p.** 135-137 ºC; **IR (film, cm^{-1})**: ν_{max} = 3264, 1639 (C=O), 1530, 760; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.93 - 7.81 (3 H, m, 3xAr*H*), 7.52 (1 H, dd, *J* = 7.1, 1.5 Hz, Ar*H*), 7.50 - 7.42 (1 H, m, Ar*H*), 7.38 - 7.28 (5 H, m, 5xAr*H*), 7.26 - 7.20 (1 H, m, Ar*H*), 5.84 (1 H, br. t, *J* = 4.8 Hz, N*H*), 4.07 – 3.64 (2 H, m, NHCH_2CH_2Ph), 3.03 ppm (2 H, t, *J* = 6.9 Hz, NHCH_2CH_2Ph); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 170.7 (C=O), 138.8 (Ar*C*), 135.7 (Ar*C*), 135.6 (Ar*C*), 133.3 (Ar*C*), 131.7 (Ar*C*), 130.7 (Ar*C*), 130.5 (Ar*C*), 128.8 (Ar*C*), 128.7 (Ar*C*), 128.6 (Ar*C*), 128.1 (Ar*C*), 128.1 (Ar*C*), 126.6 (Ar*C*), 126.5 (Ar*C*), 125.4 (Ar*C*), 119.3 (Ar*C*), 41.4 (NH*C*H_2CH_2Ph), 35.1 (NHCH_2*C*H_2Ph) ppm; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{16}BrNONa$ [M+Na$^+$]: 376.0307, found: 376.0294.

4.1.3. 2-Iodo-*N*-phenethyl-1-naphthamide (3g)

Compound **3g** was prepared according to the method of Glorius *et al.*[15] $[RhCp^*Cl_2]_2$ (9.3 mg, 0.0014 mmol, 1 mol%), $AgSbF_6$ (20.4 mg, 0.058 mmol, 4 mol%), PivOH (165 mg, 1.598 mmol), 1,2-DCE (7.3 mL), *N*-phenethyl-1-naphthamide **3d** (400 mg, 1.453 mmol) and NIS (0.360 g, 1.598 mmol). The reaction mixture was heated at 60 ºC for 16 h. The crude product was purified by flash column chromatography (70:30 Pet. Ether:EtOAc) to afford the title compound as a yellow solid (199

mg, 34%); **3g**: **R_f** (60:40 Pet. Ether:EtOAc) 0.4; **m.p.** 138-140 ºC; **IR (film, cm^{-1})**: ν_{max} = 3297, 1632 (C=O), 1538, 532; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.24 (1 H, dd, *J*=7.3, 1.1 Hz, Ar*H*), 7.89 - 7.80 (2 H, m, 2xAr*H*), 7.56 - 7.50 (1 H, m, Ar*H*), 7.47 - 7.39 (1 H, m, Ar*H*), 7.36 - 7.20 (5 H, m, 5xAr*H*), 7.15 (1 H, t, *J*=7.7 Hz, Ar*H*), 5.94 (1 H, br. t, *J*=5.2 Hz, N*H*), 3.83 (2 H, br. m, NHC*H*$_2$CH$_2$Ph), 3.03 (2 H, t, *J*=7.1 Hz, NHCH$_2$C*H*$_2$Ph) ppm; **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 169.8 (C=O), 141.9 (Ar*C*), 139.7 (Ar*C*), 138.8 (Ar*C*), 137.7 (Ar*C*), 137.4 (Ar*C*), 135.3 (Ar*C*), 131.3 (Ar*C*), 130.5 (Ar*C*), 129.7 (Ar*C*), 128.8 (Ar*C*), 128.7 (Ar*C*), 128.3 (Ar*C*), 127.1 (Ar*C*), 126.6 (Ar*C*), 125.2 (Ar*C*), 92.0 (Ar*C*-I), 41.6 (NH*C*H$_2$CH$_2$Ph), 35.0 (NHCH$_2$*C*H$_2$Ph) ppm; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{16}INONa$ [M+Na$^+$]: 424.0169, found: 424.0155.

4.2. General procedure for cyclodehydration of amides 3a-g to 1-aryl-3,4-dihydroisoquinolines 4a-g.

The cyclodehydration of amides **3a-g** was performed according to the method of Movassaghi *et al.*[14b] The experimental data for 1-(2-chlorophenyl)-3,4-dihydroisoquinoline **4a**,[26a] 1-(2-bromophenyl)-3,4-dihydroisoquinoline **4b**,[26b] and 1-(2-bromophenyl)-3,4-dihydroisoquinoline **4c**[26c] were in accordance with the literature.

4.2.1. 1-(Naphthalen-1-yl)-3,4-dihydroisoquinoline (4d)

General procedure for cyclodehydration of amides was followed. Amide **3d** (1.000 g, 3.63 mmol), trifluoromethanesulfonic anhydride (0.69 mL, 4.00 mmol), 2-chloropyridine (0.42 mL, 4.36 mmol) in dichloromethane (18 mL). The reaction mixture was refluxed for 2 h. The crude product was purified by flash column chromatography (70:30:1 Pentane:EtOAc:Et_3N) to afford the title compound as a white solid (0.752 g, 80%); **R_f** (70:30 Pet. Ether:EtOAc) 0.3; **4d: m.p.** 135-136 ºC; **IR (film, cm^{-1})**: ν_{max} = 1613 (C=O), 759; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.97 - 7.87 (2 H, m, 2xAr*H*), 7.73 (1 H, dq, *J*=8.4, 0.9 Hz, Ar*H*), 7.58 – 7.52 (2 H, m, 2xAr*H*), 7.47 (1 H, ddd, *J*=8.2, 6.8, 1.3 Hz, Ar*H*), 7.37 (2 H, tdd, *J* = 7.3, 4.7, 1.4 Hz, 2xAr*H*), 7.31 (1 H, dd, *J* = 7.5, 1.3 Hz, Ar*H*), 7.09 (1 H, td, *J*=7.5, 1.4 Hz, Ar*H*), 6.87 (1 H, dd, *J*=7.7, 1.3 Hz, Ar*H*), 4.06 (2 H, br. m., *J* = 5.2 Hz, NC*H*$_2$CH$_2$Ar), 2.98 ppm (2 H, t, *J* = 7.5 Hz, NCH$_2$C*H*$_2$Ar); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 167.7 (C=N), 137.5 (Ar*C*), 137.2 (Ar*C*), 133.8 (Ar*C*), 131.7 (Ar*C*), 131.0 (Ar*C*), 130.3 (Ar*C*), 129.0 (Ar*C*), 128.4 (Ar*C*), 127.9 (Ar*C*), 127.5 (Ar*C*), 127.1 (Ar*C*), 126.7 (Ar*C*), 126.3 (Ar*C*), 126.0 (Ar*C*), 125.8 (Ar*C*), 125.4 (Ar*C*), 48.0 (N*C*H$_2$CH$_2$Ar), 26.3 (NCH$_2$*C*H$_2$Ar) ppm; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{16}N$ [M+H$^+$]: 258.1277, found: 258.1268.

4.2.2. 1-(2-Chloronaphthalen-1-yl)-3,4-dihydroisoquinoline (4e)

General procedure for cyclodehydration of amides was followed: amide **3e** (440 mg, 1.42 mmol), trifluoromethanesulfonic anhydride (0.22 mL, 1.56 mmol), 2-chloropyridine (0.16 mL, 1.70 mmol) in dichloromethane (10 mL). The reaction mixture was refluxed for 16 h. The crude product was purified by flash column chromatography (70:30:1 Pentane:EtOAc:Et_3N) to afford the title compound as a yellow solid (363 mg, 88%); **4e: R_f** (70:30 Pet. Ether:EtOAc) 0.3; **m.p.** 112-114ºC; **IR (film, cm^{-1})**: ν_{max} = 2941, 1618 (C=N), 810, 739; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.95 (1 H, dd, *J* = 8.1, 1.4 Hz, Ar*H*), 7.85 (1 H, dd, *J* = 8.2, 1.3 Hz, Ar*H*), 7.57 (1 H, t, *J* = 7.6 Hz, Ar*H*), 7.51 (2 H, td, dd, *J* = 7.3, 1.3 Hz, 2xAr*H*), 7.39 (1 H, t, *J* = 7.8 Hz, Ar*H*), 7.34 (1 H, td, *J* = 7.4, 1.3 Hz, Ar*H*), 7.27 (1 H, d, *J* = 7.4 Hz, Ar*H*), 7.08 (1 H, td, *J*=7.6, 1.3 Hz, Ar*H*), 6.73 (1 H, d, *J*=7.7 Hz, Ar*H*), 4.07 (1 H, ddd, *J*=14.9, 8.3, 6.3 Hz, NC*H*$_A$H$_B$CH$_2$Ar), 3.96 (1 H, ddd, *J* = 15.6, 9.5, 6.1 Hz, NCH$_A$*H*$_B$CH$_2$Ar), 3.07–2.88 (2 H, m, NCH$_2$C*H*$_2$Ar) ppm; **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 169.2 (C=N), 136.9 (Ar*C*), 136.6 (Ar*C*), 135.9 (Ar*C*), 131.6 (Ar*C*), 130.9 (Ar*C*), 130.6 (Ar*C*), 129.8 (Ar*C*), 129.8 (Ar*C*), 129.2 (Ar*C*), 129.1 (Ar*C*), 128.2 (Ar*C*), 127.4 (Ar*C*), 127.4 (Ar*C*), 126.8 (Ar*C*), 126.0 (Ar*C*), 125.9 (Ar*C*), 48.0 (N*C*H$_2$CH$_2$Ar), 25.6 (NCH$_2$*C*H$_2$Ar) ppm; **HRMS** (ESI+) *m/z* calcd for$C_{19}H_{15}NCl$ [M+H$^+$]: 292.0888, found: 292.0882

4.2.3. 1-(2-Bromonaphthalen-1-yl)-3,4-dihydroisoquinoline (4f)

General procedure for cyclodehydration of amides was followed: amide **3f** (0.195 g, 0.56 mmol), trifluoromethanesulfonic anhydride (0.13 mL, 0.62 mmol), 2-chloropyridine (78 µL, 0.68 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at 45 ºC for 16 h. The crude product was purified by flash column chromatography (70:30:1 Pentane:EtOAc:Et_3N) to afford the title compound as a yellow oil (0.166 g, 90%); **4f**: **R_f** (70:30 Pet. Ether:EtOAc) 0.3; **IR (film, cm^{-1})**: ν_{max} = 2928, 1298, 821, 764; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.94 (1 H, dd, *J*=7.0, 2.5 Hz, Ar*H*), 7.89 (1 H, dd, *J*=8.2, 1.3 Hz, Ar*H*), 7.80 (1 H, dd, *J*=7.4, 1.2 Hz, Ar*H*), 7.58 - 7.50 (2 H, m, 2xAr*H*), 7.35 (1 H, td, *J*=7.4, 1.3 Hz, Ar*H*), 7.28 (2 H, m, 2xAr*H*), 7.09 (1 H, td, *J*= 7.6, 1.3 Hz, Ar*H*), 6.81 (1 H, dd, *J* = 7.6, 1.2 Hz, Ar*H*), 4.07 (2 H, m, NC*H*$_A$*H*$_B$CH$_2$Ar), 2.99 (2 H, m, NCH$_2$C*H*$_2$Ar) ppm; **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 168.5(C=N), 137.3 (Ar*C*), 136.7 (Ar*C*), 135.8 (Ar*C*), 133.1 (Ar*C*), 131.7 (Ar*C*), 130.4 (Ar*C*), 130.3 (Ar*C*), 129.9 (Ar*C*), 129.8 (Ar*C*), 128.7 (Ar*C*), 127.5 (Ar*C*), 127.2 (Ar*C*), 126.6 (Ar*C*), 126.1 (Ar*C*), 125.6 (Ar*C*), 119.7 (Ar*C*-Br), 47.8 (N*C*H$_2$CH$_2$Ar), 25.3 (NCH$_2$*C*H$_2$Ar) ppm; **HRMS** (ESI+) *m/z* calcd for$C_{19}H_{14}NBrNa$ [M+Na$^+$]: 358.0202, found: 358.0206.

4.2.4. 1-(2-Iodonaphthalen-1-yl)-3,4-dihydroisoquinoline (4g)

General procedure for cyclodehydration of amides was followed: amide **3g** (0.100 g, 0.25 mmol), trifluoromethanesulfonic anhydride (47 µL, 0.27 mmol), 2-chloropyridine (29 µL, 0.30 mmol) in dichloromethane (1.5 mL). The reaction mixture was stirred at 45 ºC for 16 h. The crude was purified by flash column chromatography (70:30:1 Pentane:EtOAc:Et_3N) to afford the title compound as a yellow oil (0.062 g, 65%); **4g**: **R_f** (70:30 Pet. Ether:EtOAc) 0.35; **IR (film, cm^{-1})**: ν_{max} = 2934, 818, 740, 713; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 8.20 (1 H, dd, *J*= 7.4, 1.3 Hz, Ar*H*), 7.96 - 7.85 (2 H, m, 2xAr*H*), 7.54 - 7.43 (2 H, m, 2xAr*H*), 7.36 (1 H, dd, *J*= 8.2, 7.0 Hz, Ar*H*), 7.29 – 7.22 (1 H, m, Ar*H*), 7.19 - 7.11 (2 H, m, 2xAr*H*), 6.87 (1 H, d, *J*=7.7 Hz, Ar*H*), 4.17 (1 H, dt, *J*=15.6, 6.2 Hz, NC*H*$_A$H$_B$CH$_2$Ar), 4.01 (1 H, ddd, *J* = 15.7, 11.2, 6.9 Hz, NCH$_A$*H*$_B$CH$_2$Ar), 3.11 - 2.92 (2 H, m, NCH$_A$H$_B$C*H*$_2$Ar) ppm; **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 167.8 (C=N), 141.8 (Ar*C*), 138.9 (Ar*C*), 137.1 (Ar*C*), 135.9 (Ar*C*), 133.1 (Ar*C*), 132.6 (Ar*C*), 130.8 (Ar*C*), 130.5 (Ar*C*), 130.2 (Ar*C*), 129.9 (Ar*C*), 128.3 (Ar*C*), 127.5 (Ar*C*), 126.9 (Ar*C*), 126.9 (Ar*C*), 125.5 (Ar*C*), 92.4 (Ar*C*-I), 48.0 (N*C*H$_2$CH$_2$Ar), 25.6 (NCH$_2$*C*H$_2$Ar) ppm; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{15}NI$ [M+H$^+$]: 384.0244, found: 384.0243.

4.3. 1-(3,4-Dihydroisoquinolin-1-yl)naphthalen-2-yl trifluoromethanesulfonate (4h)

Compound **4h** was prepared from 2-naphthol (1.33 g, 9.10 mmol) and 3,4-dihydroisoquinoline (1.19 g, 9.10 mmol) according to the synthetic route reported by Li et al.[9] The crude product was purified by flash column chromatography to afford the title compound as a clear oil (3.13 g, 85% overall yield); **R_f** (70:30:1 Pet. Ether:EtOAc:Et_3N) 0.6; **IR (film, cm^{-1})**: ν_{max} = 1618 (C=N),

1420, 1200, 1140; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.00 (1 H, d, *J*=9.0 Hz, Ar*H*), 7.95 (1 H, d, *J* = 8.1 Hz, Ar*H*), 7.70 (1 H, dd, *J*=8.4, 1.0 Hz, Ar*H*), 7.56 (1 H, ddd, *J* = 8.2, 6.8, 1.2 Hz, Ar*H*), 7.51 - 7.46 (2 H, m, 2xAr*H*), 7.38 (1 H, td, *J*=7.5, 1.3 Hz, Ar*H*), 7.31 (1 H, dd, *J*=7.5, 1.2 Hz, Ar*H*), 7.09 (1 H, td, *J*=7.5, 1.2 Hz, Ar*H*), 6.75 (1 H, dd, *J*=7.6, 1.2 Hz, Ar*H*), 4.19 - 4.05 (2 H, m, $NCH_AH_BCH_2Ar$), 3.09 - 2.93 (2 H, m, NCH_2CH_2Ar) ppm; **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C =162.7 (C=N), 144.6 (Ar*C*), 137.3(Ar*C*), 132.6 (Ar*C*), 131.6 (Ar*C*), 131.1 (Ar*C*), 129.7 (Ar*C*), 129.3 (Ar*C*), 128.4 (Ar*C*), 128.0 (Ar*C*), 127.8 (Ar*C*), 127.3 (Ar*C*), 127.3 (Ar*C*), 127.1 (Ar*C*), 126.3 (Ar*C*), 119.8 (Ar*C*), 119.4 (Ar*C*), 117.3 ($ArCSO_2CF_3$), 48.1 (NCH_2CH_2Ar), 25.7 (NCH_2CH_2Ar); **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{14}F_3NNaO_3S$ [M+Na$^+$]: 428.0539, found: 428.0544. **HPLC**: Chiralpak® AD-H, n-Hex:IPA = 80:20, T = 25 ºC; flow = 1 mL/min, λ = 254 nm, $t_{R,A}$ = 4.8 min, $t_{R,B}$ = 8.2 min.

4.4. (1-(3,4-Dihydroisoquinolin-1-yl)naphthalen-2-yl)diphenylphosphine oxide (4i)

Compound **4i** was prepared according to the method of Mikami *et al.*[17] Dimethylsulfoxide (8 mL) and diisopropylethylamine (1.29 mL, 7.4 mmol) were added to a mixture of 1-aryl-3,4-dihydroisoquinoline **4h** (600 mg, 1.48 mmol), diphenylphosphine oxide (617 mg, 2.96 mmol), palladium diacetate (33 mg, 0.15 mmol, 10 mol%), and 1,3-bis(diphenylphosphino)propane (dppp; 94 mg, 0.22 mmol, 15 mol%), and the mixture was heated with stirring at 100 ºC for 22 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with water, dried over $MgSO_4$, and concentrated again under reduced pressure. The crude product was purified by flash column chromatography (EtOAc:MeOH 95:5) to afford the title compound as a yellow solid (0.508 g, 75%); **4i**: **R_f** (95:5 EtOAc:MeOH) 0.6; **m.p.** 97-98 ºC; **IR (film, cm^{-1}):** ν_{max} = 1629 (C=N), 1196; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.88 (2 H, dd, *J*=8.6, 1.3 Hz, 2xAr*H*), 7.71 (1 H, d, *J*=8.8 Hz, Ar*H*), 7.65 - 7.50 (6 H, m, 6xAr*H*), 7.50 - 7.31 (7 H, m, 7xAr*H*), 7.23 (1 H, td, *J*=7.3, 1.0 Hz, Ar*H*), 7.17 (1 H, dd, *J*=7.3, 0.5 Hz, Ar*H*), 6.88 (1 H, td, *J*=7.4, 1.3 Hz, Ar*H*), 6.59 (1 H, d, *J*=7.1 Hz,Ar*H*), 3.81 (2 H, m, NCH_2CH_2Ar), 3.01 (1 H, dt, *J*=16.0, 8.0 Hz, $NCH_2CH_XCH_YAr$), 2.81 ppm (1 H, dt, *J*=16.0, 7.0 Hz, $NCH_2CH_XCH_YAr$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 166.3 (Ar*C*=N, d, $J(^{13}C,^{31}P)$ = 4.0 Hz), 143.3 (Ar*C*, d, $J(^{13}C,^{31}P)$) = 8.0 Hz), 136.8, 134.6, 134.6, 134.2, 133.5, 132.2, 132.1, 132.0, 132.0, 131.9, 131.4, 131.4, 130.8, 130.4, 128.6, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.7, 127.5, 127.3, 127.2, 127.1, 126.7, 126.3, 47.5 (NCH_2CH_2Ar), 25.4 (NCH_2CH_2Ar) ppm; **^{31}P {^{1}H} NMR** (162 MHz, $CDCl_3$): δ_P = 29.6 ppm. **HRMS** (ESI+) *m/z* calcd for $C_{31}H_{24}ONNaP$ [M+Na$^+$]: 480.1488, found: 480.1475. **HPLC**: (*R*,*R*)-Whelk-O1, n-Hex:IPA = 60:40, T = 50 ºC; flow = 1 mL/min, λ = 254 nm, $t_{R,A}$ = 6.8 min, $t_{R,B}$ = 10.2 min.

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